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(54) Isoquinoline derivatives and a production method therefor

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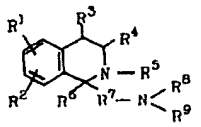
Specification

1. Title of the invention

Isoquinoline derivatives and a production method therefor

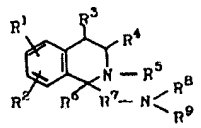
2. Scope of the patent claims

(1) Isoquinoline derivatives represented by the general formula



(in the formula, R^1 and R^2 are a hydrogen atom, hydroxyl group, acyloxy group or lower alkoxy group, and may be identical or different; R^3 and R^4 are either both hydrogen atoms, or together form a bond; R^5 is a hydrogen atom or acyl group and R^6 is a hydrogen atom, or R^5 and R^6 together form a bond; R^7 is a lower alkylene group; R^8 is a hydrogen atom or lower alkyl group; and R^9 is a lower alkyl-substituted nitrogen-containing 5-membered aromatic heterocyclic group; and when R^1 is a 6-hydroxyl group, R^2 is a 7-hydroxyl group and R^3, R^4, R^5 and R^6 are all hydrogen atoms, R^8 is a lower alkyl group) and salts thereof.

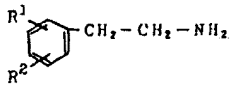
(2) A method for the production of isoquinoline derivatives represented by the general formula



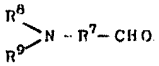
(in the formula, R^1 and R^2 are a hydrogen atom, hydroxyl group, acyloxy group or lower alkoxy group, and may be identical or different; R^3 and R^4 are either both hydrogen atoms, or together form a bond; R^5 is a hydrogen

atom or acyl group and R^6 is a hydrogen atom, or R^5 and R^6 together form a bond; R^7 is a lower alkylene group; R^8 is a hydrogen atom or lower alkyl group; and R^9 is a lower alkyl-substituted nitrogen-containing 5-membered aromatic heterocyclic group; and when R^1 is a 6-hydroxyl group, R^2 is a 7-hydroxyl group and R^3, R^4, R^5 and R^6 are all hydrogen atoms, R^8 is a lower alkyl group) and salts thereof, where

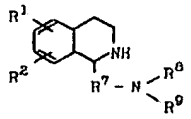
(i) a phenethylamine derivative represented by the general formula



(in the formula, R^1 and R^2 are as defined above) or a salt thereof is subjected to the action of a compound represented by the general formula

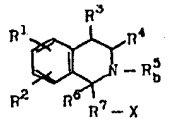


(in the formula, R^7, R^8 and R^9 are as defined above) or a reactive equivalent thereof or a salt thereof to obtain a compound represented by the general formula



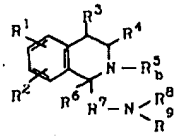
(in the formula, R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

(ii) a compound represented by the general formula



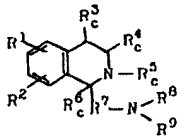
(in the formula, $R^5{}_b$ and R^6 are both hydrogen atoms, or together form a bond, X is an acid residue, and R^1, R^2, R^3, R^4 and R^7 are as defined above) or a salt thereof is subjected to the action of a compound represented by the general formula

(in the formula, R^8 and R^9 are as defined above) or a salt thereof in the presence of a base to obtain a compound represented by the general formula

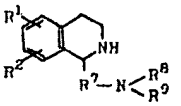


(in the formula, R^1, R^2, R^3, R^4, $R^5{}_b$, R^6, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

(iii) a compound represented by the general formula

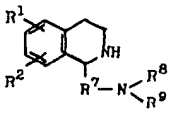


(in the formula, at least one pair from $R^3{}_c$ and $R^4{}_c$, and $R^5{}_c$ and $R^6{}_c$, together form a bond, and the other pair are either hydrogen atoms or together form a bond, and R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof is reduced to obtain a compound represented by the general formula



(in the formula, R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

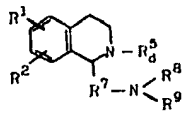
(iv) a compound represented by the general formula



(in the formula, R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof is subjected to the action of a compound represented by the general formula

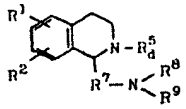
$R^5{}_d$-OH

(in the formula, $R^5{}_d$ is an acyl group) or a reactive equivalent thereof or a salt thereof to obtain a compound represented by the general formula

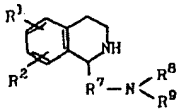


(in the formula, R^1, R^2, $R^5{}_d$, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

(v) a compound represented by the general formula

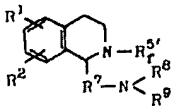


(in the formula, R^1, R^2, $R^5{}_d$, R^7, R^8 and R^9 are as defined above) or a salt thereof is subjected to an $R^5{}_d$ acyl group elimination reaction to obtain a compound represented by the general formula

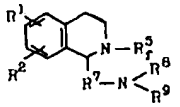


(in the formula, R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

(vi) a compound represented by the general formula

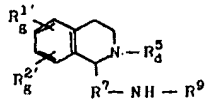


(in the formula, $R^5{}'_f$ is a protected aminoalkyl-substituted acyl group, and R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof is subjected to an amino protective group elimination reaction to obtain a compound represented by the general formula

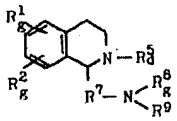


(in the formula, $R^5{}_f$ is an aminoalkyl-substituted acyl group, and R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

(vii) a compound represented by the general formula

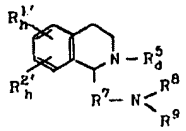


(in the formula, $R^{1'}{}_g$ and $R^{2'}{}_g$ are a hydrogen atom, hydroxyl group, lower alkoxy group or acyloxy group, and may be identical or different, and $R^5{}_d$, R^7 and R^9 are as defined above) or a salt thereof is subjected to the action of an alkylating agent to obtain a compound represented by the general formula

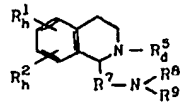


(in the formula, $R^1{}_g$ and $R^2{}_g$ are a hydrogen atom, acyloxy group or lower alkoxy group, and may be identical or different, $R^8{}_g$ is a lower alkyl group, and $R^5{}_d$, R^7, and R^9 are as defined above) or a salt thereof, or

(viii) a compound represented by the general formula

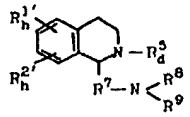


(in the formula, at least one of $R^{1'}{}_h$ and $R^{2'}{}_h$ is a hydroxyl group, and the other is a hydrogen atom, hydroxyl group, acyloxy group or lower alkoxy group, and $R^5{}_d$, R^7, R^8 and R^9 are as defined above) or a salt thereof is subjected to the action of an acylating agent to obtain a compound represented by the general formula



(in the formula, at least one of $R^1{}_h$ and $R^2{}_h$ is an acyloxy group, and the other is a hydrogen atom, lower alkoxy group or acyloxy group, and $R^5{}_d$, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

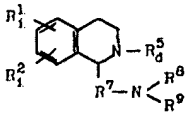
(ix) a compound represented by the general formula



(in the formula, $R^{1'}{}_h$, $R^{2'}{}_h$, $R^5{}_d$, R^7, R^8 and R^9 are as described above) or salt thereof

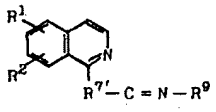
[sic: there is clearly text missing here in the original. The section is expanded further on pages 19/20]

to obtain a compound represented by the general formula

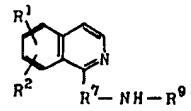


(in the formula, at least one of $R^1{}_i$ and $R^2{}_i$ is a lower alkoxy group, and the other is a hydrogen atom, acyloxy group or lower alkoxy group, and $R^5{}_d$, R^7, R^8 and R^9 are as defined above) or a salt thereof, or

(x) a compound represented by the general formula



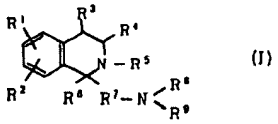
(in the formula, $R^{7'}$ is a lower alkylene group or a bond, and R^1, R^2, and R^9 are as described above) or salt thereof is reduced to obtain a compound represented by the general formula



(in the formula, R^1, R^2, R^7 and R^9 are as defined above) or a salt thereof.

3. Detailed description of the invention

The present invention relates to novel isoquinoline derivatives represented by the general formula



(I)

(in the formula, R^1 and R^2 are a hydrogen atom, hydroxyl group, acyloxy group or lower alkoxy group, and may be identical or different; R^3 and R^4 are either both hydrogen atoms, or together form a bond; R^5 is a hydrogen atom or acyl group and R^6 is a hydrogen atom, or R^5 and R^6 together form a bond; R^7 is a lower alkylene group; R^8 is a hydrogen atom or lower alkyl group; and R^9 is a lower alkyl-substituted nitrogen-containing 5-membered aromatic heterocyclic group; and when R^1 is a 6-hydroxyl group, R^2 is a 7-hydroxyl group and R^3, R^4, R^5 and R^6 are all hydrogen atoms, R^8 is a lower alkyl group), salts thereof, and a production method therefor.

In general formula (I),

examples of R^1 and R^2 acyloxy groups include lower alkanoyloxy groups such as acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy and hexanoyloxy, and aroyloxy groups such as benzoyloxy, naphthoyloxy, o-toluoyloxy, m-toluoyloxy and p-toluoyloxy.

Specific examples of R^1 and R^2 lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy,

isopentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy and isohexyloxy.

Examples of R^5 acyl groups are aroyl groups such as benzoyl, naphthoyl, toluoyl and xyloyl, aralkyloxycarbonyl groups such as benzyloxycarbonyl, phenethyloxycarbonyl and benzhydryloxycarbonyl, and cycloalkylcarbonyl groups such as cyclopentylcarbonyl, cyclohexylcarbonyl and cycloheptylcarbonyl; these acyl groups may be substituted by aminoalkyl groups such as aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl and aminohexyl, and specific examples of preferred substituted acyl groups include 4-aminomethylcyclohexylcarbonyl, 4-aminoethyl-cyclohexylcarbonyl and 4-aminopropylcyclohexylcarbonyl. Also, the amino group on the above-mentioned aminoalkyl group substituent on the acyl group may be protected by an appropriate amino-protecting group, and preferred examples of such amino-protecting groups for the R^5 acyl groups, for example, include aroyl groups, aralkoxycarbonyl groups and cycloalkylcarbonyl groups, and of these, benzyloxycarbonyl is preferred.

Specific examples of R^7 lower alkylene groups include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and propylene.

Examples of R^8 lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl and isohexyl.

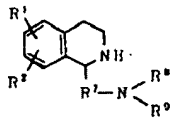
Specific examples of R^9 nitrogen-containing 5-membered aromatic heterocyclic groups are 5-membered heterocyclic groups containing from 1 to 4 nitrogen atoms, such as pyrrolyl, imidazolyl, pyrazolyl, 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl and other such triazolyls, and 1H-tetrazolyl, 2H-tetrazolyl and other such tetrazolyls.

These heterocyclic groups may be substituted at any position by lower alkyl groups such as the above-mentioned R^8 lower alkyl groups.

The salts of the isoquinoline derivatives (I) are acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid and sulfuric acid, or organic acids such as acetic acid, malic acid, tartaric acid, maleic acid and fumaric acid.

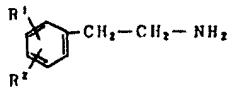
The inventive isoquinoline derivatives (I) and salts thereof can be prepared by the following methods.

(a) Compounds represented by the general formula



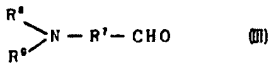
(Ia)

(in the formula, R^1, R^2, R^7, R^8 and R^9 are as defined above) and salts thereof can be produced by subjecting a phenethylamine derivative represented by the general formula



(II)

(in the formula, R^1 and R^2 are as defined above) or a salt thereof to the action of a compound represented by the general formula



(III)

(in the formula, R^7, R^8 and R^9 are as defined above) or a reactive equivalent thereof or a salt thereof.

Reactive equivalents to compound (III) are all compounds that react the same way as compound (III) in the reactions thereof; more specifically, they are 1) compound (III) formyl group derivatives, for example, in which the formyl group has been converted to an acetal, hemiacetal, hydride (diol), hydride (mono- or di-) acyl

form, thioacetal, hemithioacetal, Schiff base or tautomeric enamine, oxime, semicarbazone, thiosemicarbazone, methoxalyl, ethoxalyl or other such alkoxalyl group, 2) compounds obtained by converting the compound (III) formylmethylene group to a 2-acyloxyvinyl group such as 2-acetoxyvinyl or 2-propionyloxyvinyl, a 2-alkoxyvinyl group such as 2-methoxyvinyl, 2-ethoxyvinyl, 2-propoxyvinyl or 2-isopropoxyvinyl, a 2-alkylthiovinyl group such as 2-methylthiovinyl, 2-ethylthiovinyl or 2-propylthiovinyl, or a derivative such as a 2-aminovinyl group, and 3) compounds obtained by substituting the methylene hydrogen adjacent to the formyl group in compounds (III), or above-mentioned reactive equivalents 1) and 2), with a carboxyl group or derivative thereof, where examples of such carboxyl group derivatives are lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, and tert-butyl ester.

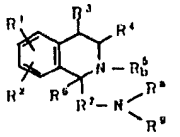
The salts of compounds (II) and (III) and reactive equivalents thereof used as starting material in this method are the same as those given as examples of salts of target compounds (I).

Inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid and hydrobromic acid, and organic acids such as acetic acid, chloroacetic acid, trifluoroacetic acid, propionic acid and methanesulfonic acid are examples of acids used when this reaction is performed in the presence of an acid. The reaction is usually performed in a solvent that does not adversely affect the reaction, such as methanol, ethanol, n-butanol or other such alcohol, or water, benzene, chloroform, or dioxane, or without a solvent, at low temperature or room temperature, or with heating to a temperature from warm to around the boiling point of the solvent; a mixture of

solvents can be used, or the reaction can proceed in a buffer solution.

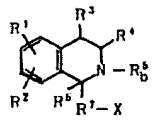
It should be noted that of starting material compounds (III), the compounds when R^8 is a lower alkyl group are novel, and can be obtained by N-alkylating the corresponding compound in which R^8 is a hydrogen atom.

(b) Compounds represented by the general formula



(Ib)

(in the formula, R^1, R^2, R^3, R^4, R^7, R^8 and R^9 are as defined above, and $R^5{}_b$ and R^6 are both hydrogen atoms or together form a bond) and salts thereof can be obtained by subjecting a compound represented by the general formula



(IV)

(in the formula, R^1, R^2, R^3, R^4, $R^5{}_b$, R^6 and R^7 are as defined above, and X is an acid residue) or a salt thereof to the action of a compound represented by the general formula

(V)

(in the formula, R^8 and R^9 are as defined above) or a salt thereof in the presence of a base.

The acid residue represented by X in starting material compound (IV) is a residue of an acid such as hydrochloric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, alkylsulfuric acid, toluenesulfonic acid, benzenesulfonic acid or dialkylcarbamic acid.

The salts of starting material compounds (IV) and (V) are the same as those given as examples of salts of compound (I).

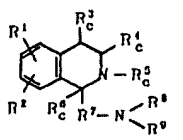
The base used in this reaction can be a hydroxide, amide, hydride, alkoxide or carbonate of an alkali metal such as sodium or potassium, or an alkaline earth metal such as magnesium or calcium, or an organic base such as pyridine. Of these bases, alkali metal hydrides such as sodium hydride and potassium hydride are particularly preferred.

This reaction can be performed in N,N-dimethylformamide, benzene, toluene, or in a lower alcohol such as methanol or ethanol, or in ether, benzene [sic], acetone, tetrahydrofuran, dioxane, acetonitrile, chloroform, methylene chloride, ethyl acetate, pyridine or water, or in another solvent that does not adversely affect the reaction, or it can be performed without a solvent.

There are no particular limitations regarding the reaction temperature, and the reaction may be performed with cooling, at room temperature, or with warming or heating.

It should be noted that the reaction starting material compounds (Ib) that are novel can, for example, be produced by method similars to that disclosed in the Journal of the American Chemical Society, volume 55, pages 2555 to 2559 (1933).

(c) Compounds represented by general formula (Ia) and salts thereof can also be produced by reducing a compound represented by the general formula



(Ic)

(in the formula, R^1, R^2, R^7, R^8 and R^9 are as defined above, and at least one pair from R^3_c and R^4_c, and R^5_c and

R^6_c, together form a bond, and the other pair are either hydrogen atoms or together form a bond) or a salt thereof.

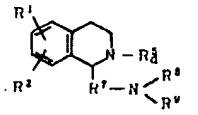
This method involves reduction by hydrogen, metal and acid, or alkali metal borohydride (sodium borohydride, potassium borohydride, etc.) or alkali metal aluminium hydride (sodium aluminium hydride, potassium aluminium hydride, etc.), in the presence of a catalytic reduction catalyst under acidic conditions.

The salts of compounds (Ic) are the same as those given as examples of salts of compounds (I).

Here, examples of the metal catalysts used for catalytic reduction are platinum oxide, palladium-carbon, rhodium and Raney nickel, and in reduction using metal and acid, examples of the metal are iron, tin and zinc, and examples of the acid are hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid, acetic acid and trichloroacetic acid, etc.

Reduction using an alkali metal borohydride or an alkali metal aluminium hydride is usually performed at room temperature or with heating, in a solvent that does not adversely affect the reaction, such as methanol, ethanol, tetrahydrofuran or dioxane.

(d) Compounds represented by the general formula


(Id)

(in the formula, R^5_d is an acyl group, and R^1, R^2, R^7, R^8 and R^9 are as defined above) and salts thereof can be obtained by subjecting an above-mentioned compound represented by general formula (Ia) or a salt thereof to the action of compound represented by the general formula

R^5_d-OH (VI)

(in the formula, R^5_d is as defined above) or a reactive derivative thereof or a salt thereof.

Examples of the acyl group R^5_d in starting material compound (VI) include the earlier examples of the compound (I) R^5_d acyl group.

Acid halides, acid anhydrides, amides, esters and the like are examples of reactive derivatives of compound (VI).

When the starting material compound (VI) is in the form of a free acid or salt thereof, it is beneficial to perform the reaction in the presence of a common coupling agent such as N,N'-dicyclohexylcarbodiimide. It should be noted that examples of salts of compounds (VI) are salts with inorganic bases, such as alkali metal salts, alkaline earth metal salts and ammonium salts, and salts with organic bases such as trimethylamine and dicyclohexylamine.

This reaction is usually performed in a solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, dimethylformamide, pyridine, and other common organic solvents that do not adversely affect the reaction, and the hydrophilic solvents here can be used mixed with water.

Moreover, the reaction may be performed in the presence of a base such as an alkali metal hydroxide, alkali metal hydrogen carbonate, alkali metal carbonate, trialkylamine, N,N-dialkylbenzylamine or pyridine, and the bases and the above-mentioned coupling agents that are liquids can also act as solvent. There are no particular limitations regarding the reaction temperature, and the reaction may proceed with ice-cooling, at room temperature, or with warming or heating.

(e) Compounds represented by the general formula (Ia) and salts thereof can also be obtained by subjecting a compound represented by the general formula (Id) or a salt thereof to an R^5_d acyl group elimination reaction.

This reaction is performed according to a common method such as reduction or elimination by the action of an acid or base, depending on the type of R^5_d acyl group and the type of substituent groups represented by R^1 and R^2.

When R^1 and R^2 are hydrogen atoms, hydroxyl groups or lower alkoxy groups (they may be identical or different), any common method involving reduction or elimination by the action of an acid or base can be employed; however, when either one of R^1 and R^2 is an acyloxy group or both R^1 and R^2 are acyloxy groups, elimination by reduction is preferred.

It should be noted that when either one of R^1 and R^2 is an acyloxy group or both R^1 and R^2 are acyloxy groups, elimination by the action of acid or base results in the elimination of said acyl group to a hydroxyl group, and this too is included in the scope of this method.

In elimination by the action of an acid, the acid used depends on the circumstances, and those that can be distilled off easily under reduced pressure, such as hydrobromic acid, hydrochloric acid, formic acid, acetic acid and trifluoroacetic acid, are most commonly used. Hydrophilic organic solvents, water and mixtures thereof are often used when a solvent is used in elimination by the action of acid.

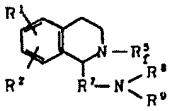
Examples of bases used for elimination by the action of a base include inorganic bases, such as hydroxides, carbonates and hydrogen carbonates of alkali metals such as sodium and potassium and alkaline earth metal such as magnesium and calcium, and organic bases such as trimethylamine, triethylamine and other such

trialkylamines, and picoline, N-methylpyrrolidine and N-methylmorpholine. Elimination reactions by the action of these bases are often performed in water, hydrophilic organic solvents or mixtures thereof.

Examples of methods of reduction, in elimination by reduction, include methods whereby an organic or inorganic acid, such as acetic acid, propionic acid or hydrochloric acid, is used with a metal such as tin or zinc, or a metal compound such as chromium dichloride or chromium acetate, and methods whereby reduction is performed in the presence of a metal catalyst for catalytic reduction; palladium catalysts are most commonly used as the metal catalyst for catalytic reduction, although other catalysts may be used.

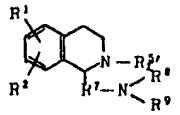
There are no particular limitations regarding the temperature of this reaction, and it can be selected as appropriate depending on the type of acyl group to be eliminated, the elimination method, and so forth.

(f) Compounds represented by the general formula



(If)

(in the formula, $R^5{}_f$ is an aminoalkyl-substituted acyl group, and R^1, R^2, R^7, R^8 and R^9 are as defined above) and salts thereof can be obtained by subjecting a compound represented by the general formula

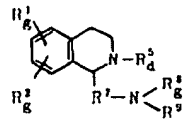


(If')

(in the formula, $R^{5'}{}_f$ is a protected aminoalkyl-substituted acyl group, and R^1, R^2, R^7, R^8 and R^9 are as defined above) or a salt thereof to elimination of the amino protective group.

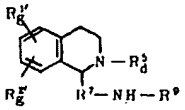
This reaction is often performed by catalytic reduction as described for above-mentioned method (e), depending on the protective group.

(g) Compounds represented by the general formula



(Ig)

(in the formula, R^1_g and R^2_g are hydrogen atoms, lower alkoxy groups or acyloxy groups, and may be identical or different, R^8_g is a lower alkyl group, and R^5_d, R^7 and R^9 are as defined above) and salts thereof can be obtained by subjecting a compound represented by the general formula



(Ig')

(in the formula, $R^{1'}_g$ and $R^{2'}_g$ are hydrogen atoms, hydroxyl groups, lower alkoxy groups or acyloxy groups, and may be identical or different, and R^5_d, R^7 and R^9 are as defined above) or a salt thereof to the action of an alkylating agent.

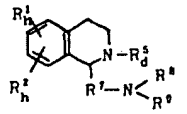
Ordinary N-alkylating agents are used as the alkylating agent, and of these, alkyl halides such as methyl iodide and ethyl iodide are preferred; when these alkyl halides are used as the alkylating agent, it is desirable to perform the reaction in the presence of a base. Alkali metal hydrides such as sodium hydride and potassium hydride are commonly used as the base.

For this reaction, the reaction conditions such as solvent and reaction temperature are the same as for above-mentioned method (d).

It should be noted that when compounds (Ig') in which $R^{1'}_g$ and (or) $R^{2'}_g$ are hydroxyl groups are used as the starting

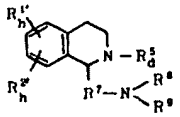
material, this reaction yields compounds (Ig) in which these hydroxyl groups are also alkylated to form lower alkoxy groups; this is also included in the scope of this method.

(h) Compounds represented by the general formula



(Ih)

(in the formula, at least one of $R^1{}_h$ and $R^2{}_h$ is an acyloxy group, and the other is a hydrogen atom, acyloxy group or lower alkoxy group, and $R^5{}_d$, R^7, R^8 and R^9 are as defined above) and salts thereof can be obtained by subjecting a compound represented by the general formula



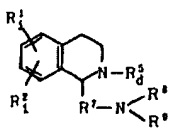
(Ih')

(in the formula, at least one of $R^{1'}{}_h$ and $R^{2'}{}_h$ is a hydroxyl group, and the other is a hydrogen atom, hydroxyl group, acyloxy group or lower alkoxy group, and $R^5{}_d$, R^7, R^8 and R^9 are as defined above) or a salt thereof to the action of an acylating agent.

Carboxylic acids having an acyl moiety such as the above-mentioned examples of R^1 and R^2 acyloxy groups, and reactive derivatives thereof, are used as the acylating agent.

This reaction is performed in the same way as above-mentioned method (d).

(i) Compounds represented by the general formula

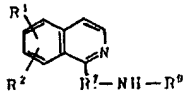


(in the formula, at least one of $R^1{}_i$ and $R^2{}_i$ is a lower alkoxy group, and the other is a hydrogen atom, acyloxy

group or lower alkoxy group, and $R^5{}_d$, R^7, R^8 and R^9 are as defined above) and salts thereof can be obtained by subjecting an above-mentioned compound (Ih') or a salt thereof to the action of an alkylating agent.

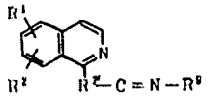
This reaction is performed in the same way as above-mentioned method (g).

(j) Compounds represented by the general formula



(Ij)

(in the formula, R^1, R^2, R^7 and R^9 are as defined above) and salts thereof can be obtained by reducing a compound represented by the general formula



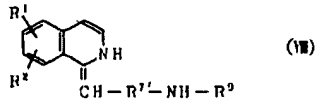
(VII)

(in the formula, $R^{7'}$ is a lower alkylene group or a bond, and R^1, R^2 and R^9 are as defined above) or a salt thereof.

Examples of salts of starting material compounds (VII) are the same as those of salts of compounds (I).

The reduction reaction in this method is preferably catalytic reduction using a metal catalyst for catalytic reduction, and the catalytic reduction is often performed in the presence of a catalyst such as those for method (c), in a solvent that does not participate in the reaction, such as methanol, ethanol, tetrahydrofuran or dioxane, at room temperature or with heating.

It should be noted that compounds represented by the general formula



(VIII)

(in the formula, R^1, R^2, $R^{7'}$and R^9 are as defined above) and salts thereof are produced as secondary products in

this reaction, and above-mentioned target substances (Ij) can be obtained by, for example, subsequent heating of these compounds in the presence of an acid such as hydroiodic acid, hydrobromic acid or hydrochloric acid; this is also included in the scope of this method.

It should be noted that in reactions where compounds (Ij) are derived from above-mentioned secondary product compounds (VIII), when the compound (VIII) R^1 or R^2 is an acyloxy group or lower alkoxy group, depending on the reaction conditions, these groups may become hydroxyl groups; this is also included in the scope of this method.

Starting material compounds (VII) used in this method are novel compounds, and can be obtained by the method disclosed in the working examples, or by a similar method.

The target compounds obtained according to all of the methods described above can be isolated and purified by common methods, and if desired, they may be obtained in the form of an above-mentioned salt, by common methods.

As illustrated by the pharmacological test data shown below, inventive target compounds (I) inhibit gastric juice secretion and are useful as medical drugs.

Test method

A few weeks before the experiment, Heidenhaim pouches were fashioned in healthy beagle dogs. For from 18 to 24 hours before each experiment, no food was administered, and water only was administered. On the day of the experiment, a venous catheter was inserted non-clinically. Pentagastrin was administered via the catheter at 10 μg/kg/h, to achieve maximum gastric juice secretion. After the secretion had reached a plateau, test substance (1 mg/kg) was injected intravenously. The amount secreted was measured at 15 minute intervals, and

the amount of acid excreted was calculated in units of μEqH^+/15 min.

Test results

The test results obtained using the compounds obtained for each working example as the test substance are shown in the table below, calculated as the maximum decrease (%) in gastric acid secretion.

Test substance (working example)	Efficacy (%)
1 (b)	90.3
3	73.9
9	67
23	85.4
24	64.1
30	83.8
34	57.6
39	87.9
40	65.9

As is clear from the results shown above, the inventive target compounds (I) are useful as anti-ulcer agents.

These inventive compounds (I) are usually administered as one dose of from 0.1 mg/kg to 500 mg/kg from 1 to 4 times a day, and they can be administered in the form of tablets, powder, dispersion, capsules, syrup, injection fluid, suppositories or the like. It should be noted that the above-mentioned dose is increased or decreased as appropriate depending on the age, weight and condition of the patient and on the method of administration. Also, all of the above-mentioned preparations can be produced by conventional methods using common carriers, additives and the like.

The invention is described below by means of working examples.

Working example 1

(a) Production of the starting material compound

(1-Methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (2.15 g) was dissolved in N,N-dimethylformamide (21 ml), methyl iodide (3 ml) was added and the system was cooled to 5°C. Sodium hydride (65%) (0.57 g) was added and the resulting system was agitated for 2 hours. Iced water was added to the reaction solution, which was then extracted twice using ethyl acetate. The ethyl acetate layers were washed once using water and once using saturated salt solution, dried using anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resulting oil was purified by silica gel column chromatography (30 g of silica gel) using ethyl acetate and chloroform (1:4) as the elution solvent, to obtain oily N-methyl-N-(1-methyl-1H-tetrazol-5-yl)amino- acetaldehyde diethyl acetal (2.18 g).

IR (film): 1580, 1450, 1060 cm^{-1}

NMR δ (ppm) ($CDCl_3$): 1.13 (6H, t, J = 7.0 Hz), 3.16 (3H, s), 3.43 (2H, d, J = 5.5 Hz), 3.56 (4H, q, J = 7.0 Hz), 3.93 (3H, s), 4.70 (1H, t, J = 5.5 Hz)

(b) Production of the target compound

Ethanol (12 ml), water (4 ml) and concentrated hydrochloric acid (0.9 ml) were added to 3,4-dihydroxyphenethylamine hydrochloride (2.84 g) and N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (4.6 g), and the system was agitated for 5 hours at 90°C. Isopropyl alcohol and ether were added to the reaction solution, and the resulting system was left to stand. The precipitated crystals were filtered and washed using isopropyl ether, to obtain crude crystals of 6,7-dihydroxy-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl).

aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.3 g). The crystals were then recrystallised from water, isopropyl alcohol and ether. Yield 1.3 g.

M.p. 237-238°C

IR (Nujol): 3600, 1590, 1528 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.93 (2H, m), 3.23 (2H, m), 3.20 (3H, s), 3.90 (2H, m), 4.03 (3H, s), 4.53 (1H, m), 6.62 (1H, s), 6.76 (1H, s), 8.5-10.3 (4H, m)

Elementary analysis: $C_{13}H_{18}N_6O_2 \cdot HCl$

Calculated values: C 47.78; H 5.86; N 25.74; Cl 10.84 (%)

Experimental values: C 47.54; H 5.78; N 25.55; Cl 10.99 (%)

Working example 2

(a) Production of the starting material compound

N,N-dimethylformamide (80 ml) was added to N-(1-methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (10.0 g) and ethyl bromide (7 ml), and the system was ice-cooled. Sodium hydride (65.5%) (2.0 g) was added a little at a time, and the resulting system was agitated for 3 hours with ice-cooling. The reaction solution was poured into 300 ml of water, sodium chloride was added and the resulting system was extracted using ethyl acetate. The ethyl acetate layer was washed using saturated salt solution, dried using anhydrous sodium sulfate, then the solvent was concentrated under reduced pressure. The resulting oily layer was separated by silica gel column chromatography (200 g of silica gel) using chloroform as the elution solvent, to obtain N-ethyl-N-(1-methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (11.7 g) as an oil.

IR (film): 1575, 1450, 1410 cm^{-1}

NMR δ (ppm) (CCl_4): 0.95-1.40 (9H, m), 3.20-3.73 (8H, m), 3.87 (3H, s), 4.55 (1H, t, J = 5.0 Hz)

(b) Production of the target compound

Ethanol (50 ml), water (20 ml) and concentrated hydrochloric acid (3.6 ml) were added to 3,4-dihydroxyphenethylamine hydrochloride (6.5 g) and N-ethyl-N-(1-methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (11.7 g), and the system was refluxed for 4 hours 30 minutes. The reaction solution was concentrated under reduced pressure to obtain an oil (16.5 g). The oil was dissolved in water (100 ml), then sodium hydrogen carbonate (11.5 g) was added and the system was ice-cooled. Benzyloxycarbonyl chloride (5.8 g) was added dropwise, keeping the reaction solution at a temperature no greater than 6°C, and the system was agitated for 2 hours at the same temperature. The precipitate was filtered, washed using water then dried, to obtain 10.5 g of oil. This oil was purified by silica gel column chromatography (200 g of silica gel) using ethyl acetate as the elution solvent, to obtain 2-benzyloxycarbonyl-1-[N-ethyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (6.75 g) as an oil.

IR (Nujol): 1690, 1580, 1520 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.03 (3H, t, J = 6.0 Hz), 2.1-2.83 (2H, m), 3.03-4.00 (6H, m), 3.66 (3H, s), 5.07 (3H, broad s), 6.53 (1H, s), 6.70 (1H, s), 7.30 (5H, s), 8.80 (2H, s)

Working example 3

2-Benzyloxycarbonyl-1-[N-ethyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (3.0 g) was dissolved in ethanol (20 ml), 10% palladium-carbon (0.6 g) was added and catalytic reduction was allowed to proceed at atmospheric pressure. N,N-dimethylformamide was added to the reaction solution, the precipitated precipitate was dissolved, and the

catalyst was filtered. Fumaric acid (0.79 g) was added to the filtrate and dissolved, the system was concentrated under reduced pressure, and the resulting residue was crystallised from isopropyl alcohol, then recrystallised from water, to obtain 1-[N-ethyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dihydroxy-1,2,3,4-tetrahydro-isoquinoline fumarate (1.3 g).

M.p. 205-207 °C

IR (Nujol): 3130, 1700, 1600, 1550, 1530 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.06 (3H, t), 2.63-2.90 (2H, m), 2.99-3.70 (6H, m), 3.93 (3H, s), 4.10-4.63 (1H, m), 6.50 (2H, s), 6.53 (1H, s), 6.70 (1H, s)

Elementary analysis: $C_{18}H_{24}N_6O_6 \cdot H_2O$

Calculated values: C 49.31; H 5.98; N 19.17 (%)

Experimental values: C 49.51; H 6.11; N 19.12 (%)

Working example 4

(a) Production of the starting material compound

N-(1-methyl-1H-tetrazol-5-yl)-N-propylaminoacetaldehyde diethyl acetal oil was obtained from N-(1-methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (10.8 g) and propyl bromide (11.3 g) by the same method as described above in Working example 2(a).

IR (film): 1570, 1450, 1410, 1380 cm^{-1}

NMR δ (ppm) (CCl_4): 0.97 (3H, t, J = 7.0 Hz), 1.10 (6H, t, J = 7.0 Hz), 1.30-1.97 (2H, m), 3.13-4.26 (8H, m), 3.83 (3H, s), 4.55 (1H, t, J = 5.0 Hz)

(b) Production of the target compound

Ethanol (20 ml) and 1N hydrochloric acid (6.5 ml) were added to 3,4-dihydrophenethylamine hydrochloride (3.1 g) and N-(1-methyl-1H-tetrazol-5-yl)-N-propylamino-acetaldehyde diethyl acetal (9.3 g) and the system was refluxed for 5 hours. The reaction solution was concentrated under reduced pressure, and the residue was neutralised by adding aqueous saturated sodium hydrogen

carbonate solution, then extracted using ethyl acetate. The ethyl acetate layer was washed using saturated salt solution and dried using anhydrous magnesium sulfate, then the solvent was distilled off to obtain an oil (7.7 g). This oil was diluted using methanol (30 ml), then fumaric acid (0.94 g) was added and dissolved. This solution was concentrated under reduced pressure, and the resulting crystalline residue was recrystallised from methanol and water to obtain 6,7-dihydroxy-1-[N-(1-methyl-1H-tetrazol-5-yl)-N-propylaminomethyl]-1,2,3,4-tetrahydroisoquinoline ½ fumarate (2.9 g).

M.p. 203-205°C

IR (Nujol): 3400, 1625, 1560, 1530 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 0.83, (3H, t, J = 7.0 Hz), 1.55 (2H, m), 2.40-4.37 (9H, m), 3.93 (3H, s), 6.43 (1H, s), 6.48 (1H, s), 6.63 (1H, s), 7.20 (4H, broad s)

Elementary analysis: $C_{15}H_{22}N_6O_2 \cdot \frac{1}{2}C_4H_4O_4 \cdot \frac{1}{2}H_2O$

Calculated values: C 52.97; H 6.54; N 21.81 (%)

Experimental values: C 52.33; H 6.60; N 21.34 (%)

Working example 5

6,7-Dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (12.2 g) was heated and dissolved in water (120 ml), and sodium hydrogen carbonate (9.84 g) and tetrahydrofuran (60 ml) were added. A tetrahydrofuran (60 ml) solution of trans-4-(benzyloxycarbonylaminomethyl)cyclohexylcarbonyl chloride (13.9 g) was added dropwise, at 4-10°C, with agitation, over a period of 1 hour. The reaction was allowed to proceed for a further 2 hours, then water (500 ml) was added and crystals were obtained by filtration. They were recrystallised from 33% aqueous ethanol, to obtain 2-[trans-4-(benzyloxycarbonylaminomethyl)cyclohexylcarbonyl]-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (17 g).

M.p. 151-153°C

IR (Nujol): 3310, 1685, 1615, 1590 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 0.6-2.0 (10H, m), 2.50-3.00 (4H, m), 3.10-3.83 (4H, m), 3.60 and 3.70 (3H, both s), 5.00 (2H, s), 5.10 and 5.50 (1H, both m), 6.50 (1H, s), 6.63 and 6.73 (1H, both s), 7.00-7.50 (2H, broad), 7.40 (5H, s), 8.50-9.00 (2H, broad)

Working example 6

2-[Trans-4-(benzyloxycarbonylaminomethyl)cyclohexyl-carbonyl]-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (2 g) was suspended in a mixture of ethanol (30 ml) and water (15 ml), 10% palladium carbon was added (500 mg), and catalytic reduction was allowed to proceed under atmospheric pressure. 6N hydrochloric acid was added to acidify the system, and the catalyst was removed by filtration. The solvent was distilled off from the filtrate, and the residue was dissolved in ethanol and crystallised, to obtain 2-[trans-4-(aminomethyl)cyclo-hexylcarbonyl]-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.0 g).

M.p. 227-231°C (degradation)

IR (Nujol): 3350, 1625, 1600 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 0.30-2.00 (10H, m), 2.00-4.00 (8H, m), 3.63 and 3.77 (3H, both s), 5.13 and 5.57 (1H, both m), 6.50 (1H, s), 6.60 and 6.73 (1H, both s), 7.0-9.0 (6H, broad)

Elementary analysis: $C_{20}H_{29}O_3N_7 \cdot HCl$

Calculated values: C 53.15; H 6.69; N 21.69 (%)

Experimental values: C 52.22; H 6.40; N 21.32 (%)

Working example 7

6,7-Dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (18.72 g)

was heated and dissolved in water (120 ml), and solid sodium hydrogen carbonate (5.04 g) was added to the resulting solution at from 40 to 50°C. The solution was ice-cooled, and sodium hydrogen carbonate (10.08 g), tetrahydrofuran (40 ml) and water (20 ml) were added. Benzyloxycarbonyl chloride (11.6 g) was added dropwise over a period of 30 minutes, then the system was agitated for 2 hours. The precipitate produced was filtered, washed using water, then washed using water-containing ethanol, to obtain 2-benzyloxycarbonyl-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (23.69 g).

M.p. 211-216°C

IR (Nujol): 3470, 3280, 1660, 1620 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.60 (2H, m), 3.0-4.3 (4H, m), 3.6 (3H, broad s), 5.0 (2H, m), 5.27 (1H, m), 6.53 (1H, s), 6.73 (1H, s), 6.8-7.6 (6H, m), 8.83 (2H, s)

Working example 8

2-Benzyloxycarbonyl-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (6.92 g) was dissolved in dry pyridine (72 ml) and ice-cooled, then pivaloyl chloride (6 ml) was added and the system was agitated. After 3 hours, more pivaloyl chloride (5 ml) was added, and the resulting system was agitated for 20 hours at room temperature. Water was added to the reaction solution, the system was agitated, and the precipitate produced was filtered and washed using water then dried, to obtain crude crystals of 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dipivaloyloxy-1,2,3,4-tetrahydroisoquinoline (8.99 g). Some of the crystals were recrystallised from methanol.

M.p. 230-235°C

IR (Nujol): 3270, 1752, 1695, 1620, 1125 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.26 (18H, s), 2.80 (2H, m), 3.0-4.3 (4H, m), 3.57 (3H, s), 4.96 (2H, m), 5.3 (1H, m), 7.03 (1H, s), 7.10 (1H, s), 7.30 (6H, m)

Elementary analysis: $C_{30}H_{38}O_6N_6$

Calculated values: C 62.26; H 6.62; N 14.52 (%)

Experimental values: C 62.25; H 6.47; N 14.51 (%)

Working example 9

2-Benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dipivaloyloxy-1,2,3,4-tetrahydroisoquinoline (8.99 g) was suspended in ethanol (100 ml) and N,N-dimethylformamide (30 ml), 10% palladium carbon (1.7 g) was added, and catalytic reduction was allowed to proceed under atmospheric pressure. After completion of the reaction, the catalyst was filtered and washed using isopropyl alcohol. Fumaric acid (1.02 g) was added to the filtrate and dissolved with heating, and the solvent was distilled off under reduced pressure. The resulting crystals were dissolved in a mixed solvent comprising methanol and water, activated charcoal was added and the system was left to stand for 5 minutes. The activated charcoal was filtered and the filtrate was concentrated and then left to stand once crystals began to precipitate. The resulting crystals were filtered, then washed using isopropyl alcohol to obtain 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dipivaloyloxy-1,2,3,4-tetrahydroisoquinoline ½ fumarate (4.6 g).

M.p. 167-170°C

IR (Nujol): 1760, 1600, 1568, 1100 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.33 (18H, s), 2.93 (2H, m), 3.17 (2H, m), 3.73 (2H, m), 3.76 (3H, s), 4.40 (1H, m), 5.60 (4H, s), 6.53 (1H, s), 7.03 (1H, s), 7.13 (1H, s), 7.50 (1H, s)

Elementary analysis: $C_{24}H_{34}N_6O_6 \cdot 1.2H_2O$

Calculated values: C 54.99; H 6.76; N 16.03

Experimental values: C 55.44; H 6.77; N 16.23

Working example 10

Dry pyridine (50 ml) was added to the 2-benzyloxycarbonyl-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (5.0 g) obtained in Working example 7, and the system was ice-cooled. p-Toloyl chloride (3.7 ml) was added dropwise, the system was agitated at room temperature, and 12 hours later more p-toloyl chloride (0.6 ml) was added and the resulting system was agitated for a further 5 hours at room temperature. The reaction solution was poured into water (250 ml) and the precipitated crystals were filtered and washed using water. The resulting crystals were recrystallised from acetonitrile and dioxane to obtain 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl) aminomethyl]-6,7-bis(p-toloyloxy)-1,2,3,4-tetrahydroisoquinoline (3.35 g).

M.p. 240-242°C

IR (Nujol): 3250, 3210, 3120, 1730, 1690, 1605, 1500 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.36 (6 H, s), 2.70-3.20 (2H, m), 3.66 (3H, s), 3.20-4.50 (4H, m), 4.90-5.27 (2H, m), 5.30-5.70 (1H, m), 7.0-7.6 (6H, m), 7.37 (5H, s), 7.90 (4H, d, J = 8.0 Hz)

Working example 11

N,N-dimethylformamide (30 ml) and ethanol (15 ml) were added to the 2-benzyloxycarbonyl-1-(1-methyl-1H-tetrazol-5-yl)aminomethyl-6,7-bis(p-toloyloxy)-1,2,3,4-tetrahydroisoquinoline (2.3 g) obtained in Working example 10, and the resulting system was catalytically reduced under atmospheric pressure using 10% palladium carbon (1.2 g). After the reaction, the catalyst was filtered, concentrated hydrochloric acid (1 ml) was added to the filtrate and the system was concentrated under reduced pressure to obtain a crystalline residue. These crystals

were recrystallised from methanol, water and N,N-dimethylformamide to obtain 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-bis(p-toloyloxy)-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.4 g).

M.p. 246-248°C

IR (Nujol): 3200, 3120, 1750, 1730, 1625, 1495 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.37 (6H, s), 2.97-4.27 (6H, m), 3.87 (3H, s), 4.67-5.13 (1H, m), 7.37 (4H, d, J = 8.0 Hz), 7.50 (1H, s), 7.60 (1H, s), 7.90 (4H, d, J = 8 Hz), 9.98 (2H, broad s)

Elementary analysis: $C_{28}H_{28}N_6O_4 \cdot HCl$

Calculated values: C 61.25; H 5.32; N 15.31; Cl 6.46 (%)

Experimental values: C 61.11; H 5.20; N 15.31; Cl 6.47 (%)

Working example 12

The 6,7-dihydroxy-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (19.3 g) obtained in Working example 1(b) was heated and dissolved in water (100 ml), sodium hydrogen carbonate (12 g) was added and the system was agitated. The solution was cooled to 5°C, and water (50 ml), tetrahydrofuran (50 ml) and sodium hydrogen carbonate (12 g) were added. Benzyloxycarbonyl chloride (12.1 g) was added dropwise over a period of 30 minutes, then the system was agitated for 1 hour 10 minutes at 5°C, to produce an oil. The reaction solution was extracted 3 times using ethyl acetate, the ethyl acetate layers were collected, washed once using water and once using saturated salt solution, dried using anhydrous magnesium sulfate, then the solvent was concentrated under reduced pressure to obtain 2-benzyloxycarbonyl-6,7-dihydroxy-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline oil (29 g).

IR ($CHCl_3$): 3300, 1685, 1590, 1520 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.60 (2H, m), 2.8-4.2 (4H, m), 3.13 (3H, s), 3.80 (3H, s), 5.06 (2H, s), 5.26 (1H, m), 6.56 (1H, s), 6.70 (1H, s), 7.30 (5H, broad s), 8.80 (2H, broad s)

Working example 13

Dry pyridine (110 ml) was added to 2-benzyloxycarbonyl-6,7-dihydroxy-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (26.8 g) and the system was cooled to 5°C. Pivaloyl chloride (19 ml) was added dropwise over a period of 5 minutes, then the system was agitated for 2 hours 20 minutes at 5°C. More pivaloyl chloride (6 ml) was added to the reaction solution and the system was agitated for 14 hours at room temperature. Water was added to the reaction solution then the system was extracted 3 times using ethyl acetate. The ethyl acetate layers were collected, washed twice using water and once using saturated salt solution, dried using anhydrous magnesium sulfate, then the solvent was concentrated under reduced pressure to obtain an oil. This oil was purified by silica gel column chromatography (150 g of silica gel) using methylene chloride as the elution solvent, to obtain 2-benzyloxycarbonyl-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-bis(pivaloyloxy)-1,2,3,4-tetrahydroisoquinoline oil (41 g).

IR ($CHCl_3$): 1750, 1690, 1585 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.30 (18H, s), 2.83 (2H, m), 3.13 (3H, m), 3.0-4.0 (4H, m), 3.80 (3H, s), 5.08 (2H, s), 5.46 (1H, m), 7.1 (1H, s), 7.26 (1H, s), 7.40 (5H, s)

Working example 14

2-Benzyloxycarbonyl-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-bis(pivaloyloxy)-1,2,3,4-tetrahydroisoquinoline (10 g) was dissolved in ethanol (100 ml) and water (30 ml), 10% palladium carbon (2.0 g) was

added, and catalytic reduction was allowed to proceed for 2 hours under atmospheric pressure. The catalyst was filtered, washed using ethanol, and fumaric acid (1.95 g) was added to the filtrate and dissolved with heating. The solution was concentrated to approximately 80 ml under reduced pressure, then left to stand. The precipitated crystals were filtered, then recrystallised from methanol and water to obtain 1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-bis(pivaloyloxy)-1,2,3,4-tetrahydroisoquinoline fumarate (4.5 g).

M.p. 222-225°C

IR (Nujol): 1758, 1700, 1590, 1118, 1100 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.26 (18H, s), 2.86 (2H, m), 3.10 (2H, m), 3.13 (3H, s), 3.76 (2H, m), 3.93 (3H, s), 4.50 (1H, m), 6.53 (2H, s), 7.07 (1H, s), 7.20 (1H, s), 8.33 (3H, broad s)

Elementary analysis: $C_{17}H_{38}N_6O_8$

Calculated values: C 56.43; H 6.67; N 14.63(%)

Experimental values: C 56.08; H 6.71; N 14.79 (%)

Working example 15

N,N-dimethylformamide (60 ml) was added to the 2-benzyloxycarbonyl-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (6.92 g) obtained in Working example 7, and anhydrous potassium carbonate (16.56 g), and the system was cooled to 5°C. Methyl iodide (8 ml) was added, and the system was agitated and gradually returned to room temperature. After 23 hours, iced water was added to the reaction solution, the resulting system was agitated, and the precipitated crystals were filtered and washed using water to obtain 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6.0 g). A small amount of the crystals

were recrystallised from N,N-dimethylformamide, water and methanol.

M.p. 193-198°C

IR (Nujol): 3270, 1685, 1615, 1460 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.73 (2H, m), 3.0-4.3 (4H, m), 3.6 (3H, s), 3.73 (6H, s), 4.96 (2H, m), 5.26 (1H, m), 6.73 (1H, s), 6.83 (1H, s), 6.9-7.5 (6H, m)

Elementary analysis: $C_{22}H_{26}N_6O_4 \cdot 0.25H_2O$

Calculated values: C 59.90; H 5.97; N 18.98 (%)

Experimental values: C 60.05; H 5.72; N 18.61 (%)

Working example 16

Concentrated hydrochloric acid (5 ml), water (10 ml) and n-butanol (5ml) were added to 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.9 g) and the system was agitated for 9 hours at 100°C. After 4 hours, more concentrated hydrochloric acid (5 ml) was added. The reaction solution was concentrated and recrystallised from methanol and isopropyl alcohol to obtain 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.6 g). Some was recrystallised from water, isopropyl alcohol and methanol.

M.p. 195-205°C

IR (Nujol): 3600, 3300, 1608, 1515 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 3.0 (2H, m), 3.43 (2H, m), 3.80 (2H, m), 3.73 (6H, s), 3.80 (3H, s), 4.66 (1H, m), 6.80 (1H, s), 6.90 (1H, s), 7.70 (1H, m), 9.3-10.3 (2H, m)

Elementary analysis: $C_{14}H_{20}N_6O_2 \cdot HCl \cdot 0.5H_2O$

Calculated values: C 48.07; H 6.19; N 24.02; Cl 10.13

Experimental values: C 48.22; H 6.26; N 24.23; Cl 10.44

Working example 17

The 2-benzyloxycarbonyl-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline

(3.46 g) obtained in Working example 7 was dissolved in N,N-dimethylformamide (35 ml), the resulting system was cooled to 7°C, and methyl iodide (3.0 ml) was added. Sodium hydride (65%) (1.2 g) was added a little at a time over a period of 20 minutes, then the system was agitated for 4 hours 30 minutes at 5°C. Ammonium chloride (2.1 g) was added to the reaction solution and the resulting system was agitated for 5 minutes, then water was added and the system was agitated. The precipitate produced was filtered then washed using water to obtain 2-benzyloxycarbonyl-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (3.65 g).

Some was recrystallised from N,N-diformamide [sic] and water.

M.p. 182-184°C

IR (Nujol): 1700, 1595, 1458 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.53 (2H, m), 3.20 (2H, m), 3.5-4.0 (2H, m), 3.76 (12H, broad s), 5.07 (2H, broad s), 5.3 (1H, m), 6.76 (1H, s), 6.76 (1H, s), 6.86 (1H, s), 7.30 (5H, s)

Elementary analysis: $C_{23}H_{28}N_6O_4$

Calculated values: C 61.05; H 6.24; N 18.57

Experimental values: C 61.82; H 6.64; N 17.66

Working example 18

The 2-benzyloxycarbonyl-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (2.95 g) obtained in Working example 17 was suspended in ethanol (60 ml) and N,N-dimethylformamide (25 ml), 10% palladium-carbon (0.75 g) was added and catalytic reduction was allowed to proceed under atmospheric pressure. The disappearance of the starting material was confirmed by silica gel thin layer chromatography, then the catalyst was filtered and washed

using isopropyl alcohol. Fumaric acid (0.46 g) was added to the filtrate and dissolved, and the system was concentrated under reduced pressure. The resulting crude crystals were recrystallised from water and isopropyl alcohol to obtain 1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fumarate (1.3 g).

M.p. 188-192°C

IR (Nujol): 1700, 1585, 1512 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.90 (2H, m), 3.20 (2H, m), 3.17 (3H, s), 3.80 (2H, m), 3.73 (6H, s), 3.93 (3H, s), 4.50 (1H, m), 6.47 (2H, s), 6.73 (1H, s), 6.80 (1H, s), 8.36 (3H, broad s)

Elementary analysis: as $C_{19}H_{26}N_6O_6$

Calculated values: C 52.52; H 6.00; N 19.35 (%)

Experimental values: C 52.55; H 6.03; N 19.37 (%)

Working example 19

3-Hydroxy-4-methoxyphenethylamine hydrochloride (2.9 g), (1-methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (4.0 g) and concentrated hydrochloric acid (1.6 ml) were added to a mixture of ethanol (14 ml) and water (5.7 ml), and the system was refluxed for 3 hours. After cooling, the precipitated crystals were obtained by filtration, washed using ethanol then recrystallised from water-containing isopropyl alcohol, to obtain 6-hydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.9 g).

M.p. 240-242°C (degradation)

IR (Nujol): 3350, 1615, 1520 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.70-3.20 (2H, broad), 3.20-3.60 (2H, broad), 3.60-4.10 (2H, broad), 3.77 (3H, s), 3.83 (3H, s), 4.60 (1H, broad), 6.63 (1H, s), 6.83 (1H, s), 7.63 (1H, t, J = 6 Hz), 9.00-10.00 (3H, broad)

Elementary analysis: $C_{13}H_{18}O_2N_6 \cdot HCl$

Calculated values: C 47.78; H 5.86; N 25.72

Experimental values: C 47.43; H 5.90; N 25.97

Working example 20

Trifluoroacetic acid (70 ml) was added to 4-benzyloxy-3-methoxyphenethylamine hydrochloride (29.4 g) and (1-methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (21.5 g), and the system was heated for 3 hours 30 minutes at 92°C. The reaction solution was concentrated under reduced pressure, methanol (300 ml) was added to the resulting residue, and the system was refluxed. Activated charcoal (0.5 g) was added to this solution, and after agitation, the system was filtered and the filtrate was concentrated under reduced pressure to approximately half of its volume. The resulting solution was cooled to yield 6.3 g of crystals. The mother liquor was concentrated to obtain a further 2.1 g of crystals. These crystals were collected and dissolved in methanol (375 ml) with heating, then after treatment with activated charcoal (0.4 g), they were concentrated under reduced pressure to approximately 75 ml and left to stand at room temperature, to obtain 6.7 g of crystals. The mother liquor was concentrated to obtain a further 0.8 g of crystals. These crystals were collected and dissolved in methanol (270 ml) with heating, then activated charcoal (0.35 g) was added and the resulting system was agitated. The activated charcoal was filtered and the system was concentrated under reduced pressure then left to stand, to obtain 7-hydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (6.6 g).

M.p. 240-242°C (degradation)

IR (Nujol): 1675, 1620, 1400 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 3.06 (2H, m), 3.43 (2H, m), 3.83 (3H, s), 3.86 (3H, s), 3.80 (2H, m), 4.63 (1H, m), 6.83 (2H, s), 7.66 (1H, broad t, J = 5.0 Hz), 9.0-9.8 (3H, m)

Elementary analysis: $C_{13}H_{18}N_6O_2 \cdot HCl$

Calculated values: C 47.78; H 5.86; N 25.72; Cl 10.85

Experimental values: C 48.08; H 5.93; N 26.03; Cl 10.98

Working example 21

Acetic anhydride (5.67 g) was added, with ice-cooling, to a pyridine (40 ml) solution of the 2-[trans-4-(benzyloxycarbonylaminomethyl)cyclohexylcarbonyl]-6,7-dihydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (10.1 g) obtained in Working example 5. The system was gradually returned to room temperature and the reaction was allowed to proceed for 16 hours. Water (200 ml) was added, and crystals were obtained by filtration, air-dried then recrystallised from ethanol to obtain 6,7-diacetoxy-2-[trans-4-(benzyloxycarbonylaminomethyl)cyclohexylcarbonyl]-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (8.4 g).

M.p. 165.5-168°C

IR (Nujol): 3380, 3270, 1750, 1710, 1600 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 0.50-1.80 (10H, m), 2.30 (6H, s), 2.50-3.10 (4H, m), 3.40-4.00 (4H, m), 3.63 and 3.73 (3H, both s), 5.03 (2H, s), 5.30 and 5.75 (1H, both broad), 7.10 (1H, s), 7.17 and 7.23 (1H, both s), 7.35 (5H, s)

Working example 22

6,7-Diacetoxy-2-[trans-4-(benzyloxycarbonylaminomethyl)cyclohexylcarbonyl]-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (6.5 g) and 10% palladium carbon (1.2 g) were added to ethanol (250 ml), and catalytic reduction was allowed to proceed under atmospheric pressure. The catalyst was removed by filtration, the solvent was distilled off under reduced pressure, water was added to the residue, and the

resulting crystals were obtained by filtration then recrystallised twice from water-containing ethanol to obtain 7-actetoxy-2-[trans-4-(aminomethyl)cyclohexyl-carbonyl]-6-hydroxy-1-[(1-methyl-1H-tetrazol-5-yl)amino-methyl]-1,2,3,4-tetrahydroisoquinoline (1.3 g).

M.p. 179-183°C (degradation)

IR (Nujol): 3320, 1610, 1590 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 0.50-1.80 (10H, broad), 1.75 (3H, s), 2.45-3.00 (6H, m), 3.30-3.80 (2H, m), 3.60 and 3.70 (3H, both s), 5.10 and 5.50 (1H, both m), 6.50 (1H, s), 6.63 and 6.73 (1H, both s), 7.70 (1H, broad)

Elementary analysis: $C_{22}H_{31}O_4N_7$

Calculated values: C 57.75; H 6.83; N 21.43

Experimental values: C 58.32; H 7.05; N 21.36

Working example 23

(1-Methyl-1H-tetrazol-5-yl)aminoacetaldehyde diethyl acetal (6.30 g) and 3-hydroxyphenethylamine hydroiodide (5.97 g) were added to a mixture of ethanol (26 ml) and water (10 ml) and dissolved by agitation and heating. Concentrated hydrochloric acid (3.3 ml) was added to this solution, and the resulting system was heated under reflux for 6 hours 25 minutes. The solvent was distilled off under reduced pressure and the residue was dissolved in isopropyl alcohol with heating. This solution was left to cool, and the precipitated crystals were obtained by filtration and dried. These crystals (4.0 g) were dissolved in a small amount of water with heating, aqueous saturated sodium hydrogen carbonate solution was added to regulate the pH to 7-8, and the white precipitate produced was obtained by filtration and dried. This white powder was suspended in water (100 ml), concentrated hydrochloric acid was added and the system was agitated then cooled to room temperature, after which the precipitate was obtained by filtration and dried.

These crude crystals were recrystallised from a mixed solvent comprising water and isopropyl alcohol, to obtain white, needle-like crystals (2.5 g). They were then recrystallised from a mixed solvent comprising water and isopropyl alcohol, and dried under reduced pressure at 60°C for 13 hours to obtain white, needle-like crystals of 6-hydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.3 g).

M.p. 239.5-242°C (degradation)

IR (Nujol): 3500, 3400, 3220, 3140, 2770, 1618 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.73-3.20 (2H, m), 3.20-3.60 (2H, m), 3.60-4.10 (2H, m), 3.82 (3H, s), 4.63 (1H, t, J = 6 Hz), 6.63 (1H, s), 6.70 (1H, dd, J = 10 Hz, 2 Hz) , 7.18 (1H, d, J = 10 Hz), 7.50-7.80 (1H, m), 9.62 (2H, s)

Elementary analysis: $C_{12}H_{16}N_6O \cdot HCl$

Calculated values: C 48.57; H 5.78; N 28.32 (%)

Experimental values: C 47.58; H 5.85; N 27.79 (%)

Working example 24

The N-methyl-N-(1-methyl-1H-tetrazol-5-yl)amino-acetaldehyde diethyl acetal (1.61 g) obtained in Working example 1(a) and 3-hydroxyphenethylamine hydrochloride (1.00 g) were added to a mixture of ethanol (4.3 ml) and water (1.7 ml), and dissolved by agitation with heating. Concentrated hydrochloric acid (1.0 ml) was added to this solution, and the system was refluxed for 5 hours 50 minutes. The solvent was distilled off and the residue was passed through a column packed with HP-20 (adsorbent resin, Mitsubishi Kasei, 150 ml). The solvent of the cold water elution part was concentrated under reduced pressure, isopropyl alcohol was added and the precipitated crystals were obtained by filtration. These crystals were recrystallised from a mixed solvent comprising water and isopropyl alcohol, then dried for 8 hours at 60°C under reduced pressure to obtain white

crystals of 6-hydroxy-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (327 mg).

M.p. 235°C (degradation)

IR (Nujol): 3250, 1610, 1595, 1580 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.76-3.60 (4H, m), 3.17 (3H, s), 3.67-4.20 (2H, m), 4.05 (3H, s), 4.46-4.90 (1H, m), 6.67 (1H, s), 6.73 (1H, dd, J = 8 Hz, 1 Hz), 7.20 (1H, d, J = 8 Hz), 9.65 (2H, s)

Elementary analysis: $C_{13}H_{18}ON_6 \cdot HCl$

Calculated values: C 50.24; H 6.16; N 27.04 (%)

Experimental values: C 49.78; H 6.06; N 26.79 (%)

Working example 25

6-Hydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (8.20 g) was added to water (57 ml) and dissolved by agitating and heating at approximately 70°C. Sodium hydrogen carbonate (4.1 g) and tetrahydrofuran were added to this solution, and the system was then cooled using iced water. More sodium hydrogen carbonate (4.2 g) was added, and benzyloxycarbonyl chloride (6.19 g) was added dropwise at an internal temperature no greater than 10°C. The system was agitated for 2 hours 40 minutes with iced water-cooling, then the white precipitate produced was obtained by filtration under reduced pressure, and washed using water and ethanol. The white powder was dried for 10 hours at room temperature under reduced pressure to obtain 2-benzyloxycarbonyl-6-hydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (10.75 g).

M.p. 232-234°C (degradation)

IR (Nujol): 3440, 3300, 3250, 3130, 1660, 1610 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.63-3.03 (2H, m), 3.03-4.43 (4H, m), 3.63 (3H, m), 5.02 (2H, d, J = 5.5 Hz), 5.30 (1H, t,

J = 7.5 Hz), 6.62 (1H, s), 6.68 (1H, dd, J = 10Hz, 2.4 Hz) 6.90-7.60 (6H, m)

Working example 26

Methyl iodide (1.62 g) and calcium carbonate powder (1.57 g) were added to a dimethylformamide (30 ml) solution of 2-benzyloxycarbonyl-6-hydroxy-1-(1-methyl-1H-tetrazol-5-yl)aminomethyl-1,2,3,4-tetrahydroisoquinoline (3 g), and the system was agitated with heating for 9 hours 30 minutes at approximately 80°C. The reaction solution was poured into iced water, and the white precipitate produced was obtained by filtration then washed using water and ethanol. It was dried at room temperature under reduced pressure to obtain 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline white powder (2.63 g).

M.p. 197-201°C (degradation)

IR (Nujol): 3270, 1682, 1620 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.63-3.03 (2H, m), 3.03-4.46 (4H, m), 3.63 (3H broad s), 3.75 (3H, s), 4.86-5.17 (2H, m), 5.17-5.60 (1H, m), 5.53-7.67 (9H, m)

Working example 27

10% palladium-carbon (100 mg) was added to a dimethylformamide (40 ml) solution of 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1.02 g), and the system was agitated for 4 hours 50 minutes under a current of hydrogen. The catalyst was removed by filtration using powder filter paper. The N,N-dimethylformamide solution was concentrated under reduced pressure, ethanol was added and again the catalyst was removed by filtration using powder filter paper. The solvent was distilled off under reduced pressure, and the resulting crude crystals were recrystallised from a mixed solvent comprising ethanol and N,N-dimethylformamide, then dried for 5 hours

at 60°C under reduced pressure to obtain white crystals of 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (191 mg).

M.p. 161-162°C

IR (Nujol): 3340, 3180, 3100, 1605 cm^{-1}

NMR δ (ppm) ($CDCl_3$): 2.60-3.26 (4H, m), 3.46-4.33 (2H, m), 3.73 (3H, s), 3.80 (3H, s), 5.16 (1H, m, W1/2 = 14 Hz), 6.67 (1H, s), 6.74 (1H, dd, J = 9 Hz, 2 Hz), 7.16 (1H, d, J = 9 Hz)

Elementary analysis: $C_{13}H_{18}ON_6$

Calculated values: C 56.92; H 6.61; N 30.64 (%)

Experimental values: C 55.54; H 6.35; N 30.27 (%)

Working example 28

The 2-benzyloxycarbonyl-6-hydroxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (3.0 g) obtained in Working example 25 was suspended in pyridine (30 ml), and pivaloyl chloride (1.1 g) was added dropwise with agitation and ice-cooling. After the dropwise addition, the system was agitated for 5 hours 40 minutes at from 80 to 100°C. The reaction solution was poured into iced water (120 ml) and the white precipitate produced was obtained by filtration, and washed using water and ethanol. Drying under reduced pressure yielded 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-pivaloyloxy-1,2,3,4-tetrahydroisoquinoline (3.49 g) white powder.

M.p. 217-218°C (degradation)

IR (Nujol): 3252, 1742, 1680, 1620 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.28 (9H, s), 2.62-3.00 (2H, m), 3.08-4.35 (4H, m), 3.58 (3H, broad s), 4.78-5.12 (2H, m), 5.18-5.56 (1H, m), 6.81-7.48 (8H, m)

Working example 29

10% palladium-carbon (0.74 g) was added to an N,N-dimethylformamide (150 ml) solution of the 2-benzyl-

oxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-pivaloyloxy-1,2,3,4-tetrahydroisoquinoline (7.37 g) obtained in Working example 28, and the system was agitated for 3 hours 30 minutes under a current of hydrogen. The catalyst was separated by filtration using powder filter paper. The same operation was then repeated twice. The dimethylformamide solution was concentrated to approximately 30 ml under reduced pressure, ethanol (100 ml) was added, and the precipitated crystals were obtained by filtration. These crystals were then recrystallised from ethanol (100 ml) and dried under reduced pressure to obtain 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-pivaloyloxy-1,2,3,4-tetrahydro-isoquinoline (3.82 g).

M.p. 156-158°C (degradation)

IR (Nujol): 3250, 1742, 1618 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 1.30 (9H, s), 2.56-3.22 (4H, m), 3.22-3.84 (2H, m), 3.74 (3H, s), 4.00-4.20 (1H, m), 6.79 (1H, s), 3.86 (1H, dd, J = 8 Hz, 3 Hz), 7.26 (1H, d, J = 8 Hz)

Working example 30

1-[(1-Methyl-1H-tetrazol-5-yl)aminomethyl]-6-pivaloyloxy-1,2,3,4-tetrahydroisoquinoline (282 mg) was dissolved in ethanol (5 ml) with heating, an ethanol (5 ml) solution of oxalic acid (54.4 mg) was added dropwise to this solution with cooling, and the white precipitate produced was obtained by filtration. This was then recrystallised from a mixed solvent comprising ethanol and N,N-dimethylformamide, and dried for 12 hours at 60°C under reduced pressure to obtain white crystals of 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-pivaloyloxy-1,2,3,4-tetrahydroisoquinoline ½ oxalate (207 mg).

M.p. 236-237°C (degradation)

IR (Nujol): 3220, 1758, 1615, 1600 cm^{-1}

Elementary analysis: $C_{17}H_{24}O_2N_6 \cdot \frac{1}{2}C_2H_2O_4$

Calculated values: C 55.52; H 6.47; N 21.58 (%)

Experimental values: C 55.27; H 6.44; N 21.46 (%)

Working example 31

The 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl) aminomethyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (2.35 g) obtained in Working example 25 was suspended in pyridine (35 ml), and 4-toluoyl chloride (1.01 g) was added dropwise with agitation and ice-cooling. After the dropwise addition, the system was agitated for 20 minutes at room temperature, then agitated and heated for 6 hours at approximately 80°C. The reaction solution was poured into iced water (100 ml) and the white precipitate produced was obtained by filtration. This powder was recrystallised from a mixed solvent comprising N,N-dimethylformamide and isopropyl alcohol, then dried with heating under reduced pressure to obtain white crystals of 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl) aminomethyl]-6-(p-toluoyloxy)-1,2,3,4-tetrahydro-isoquinoline (2.61 g).

M.p. 233-235°C (degradation)

IR (Nujol): 1715, 1680, 1620 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.73-3.18 (2H, m), 3.18-4.40 (4H, m), 3.65 (3H, broad s), 4.90-5.20 (2H, m), 5.20-5.70 (1H, m), 7.0-7.63 (10H, m), 8.06 (2H, d, J = 8 Hz)

Working example 32

10% palladium-carbon (258 mg) was added to an N,N-dimethylformamide (80 ml) solution of 2-benzyloxy-carbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-6-(p-toluoyloxy)-1,2,3,4-tetrahydroisoquinoline (2.59 g), and the system was agitated for 3 hours 10 minutes under a flow of hydrogen. The catalyst was separated by filtration using powder filter paper, and the filtrate was concentrated under reduced pressure, then ethanol was

added and the precipitated crystals were obtained by filtration. These crystals were dissolved, with heating, in a mixed solvent comprising ethanol and N,N-dimethylformamide, and filtered when hot. The filtrate was left to cool and the precipitated crystals were obtained by filtration. These crystals were recrystallised from a mixed solution comprising ethanol and N,N-dimethylformamide, and white crystals of 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)amino-methyl]-6-(p-toluoyloxy)-1,2,3,4-tetrahydroisoquinoline (0.6 g) were recovered. The filtrate was then concentrated under reduced pressure, ethanol was added, and the precipitated crystals were obtained by filtration then dried for 8 hours at 50°C under reduced pressure, to obtain white crystals of 1-[(1-methyl-1H-tetrazol-5-yl) aminomethyl]-6-(p-toluoyloxy)-1,2,3,4-tetrahydroiso-quinoline (303 mg).

M.p. 178-180°C (degradation)

IR (Nujol): 3290, 3150, 1730, 1605 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.67-3.86 (6H, m), 3.76 (3H, s), 4.03-4.33 (1H, m), 6.86-7.60 (5H, m), 8.00 (2H, d, J = 8 Hz)

Working example 33

1-Methyl-1H-tetrazol-5-amine (1.98 g) was dissolved in N,N-dimethylformamide (45 ml), cooled to 5°C, then sodium hydride (65%) (0.9 g) was added and the system was agitated for 50 minutes. In a separate operation, 1-chloromethyl-3,4-dihydroisoquinoline hydrochloride (4.32 g) was dissolved in water, and this was neutralised using sodium hydrogen carbonate, then extracted 3 times using toluene. The toluene layers (approximately 15 ml) were washed using saturated salt solution, then dried using anhydrous magnesium sulfate. The N,N-dimethylformamide solution of 1-methyl-1H-tetrazol-5-amine obtained earlier

was cooled to -30°C and exchanged using nitrogen gas. The toluene solution obtained as described above was added to this solution over a period of 10 minutes, and the system was agitated for 1 hour 30 minutes at from -5°C to -15°C. Ethanol (15 ml) and sodium borohydride (1.2 g) were added to the reaction solution, and the system was agitated for 1 hour 30 minutes at 0°C. The reaction solution was cooled to from -20°C to -30°C, and acidified by the dropwise addition of concentrated hydrochloric acid, then the solvent was concentrated under reduced pressure. Water was added to the residue, and the resulting system was neutralised using sodium hydrogen carbonate and extracted 3 times using methylene chloride. The methylene chloride layers were extracted 3 times using 2N hydrochloric acid, and the aqueous layers were collected and concentrated under reduced pressure to obtain an oil. Water (30 ml) and tetrahydrofuran (10 ml) were added to the resulting oil, and the system was agitated with ice-cooling. Sodium hydrogen carbonate (9 g) was added, then benzyloxycarbonyl chloride (4.5 g) was added dropwise, and the system was agitated for 2 hours at 5°C. Ethyl acetate was added to the reaction solution, and the precipitate produced in the ethyl acetate layer was filtered then washed using ethyl acetate to obtain 2-benzyloxycarbonyl-1-[(1-amino-1H-tetrazol-5-yl)amino-methyl]-1,2,3,4-tetrahydroisoquinoline (1.94 g).

M.p. 207-210°C

IR (Nujol): 3270, 1688, 1618, 1452 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.83 (2H, m), 3.0-4.3 (4H, m), 3.60 (3H, broad s), 5.00 (2H, m), 5.40 (1H, m), 7.3 (9H, m)

Working example 34

Acetic acid (2 ml) and concentrated hydrochloric acid (2 ml) were added to the 2-benzyloxycarbonyl-1-[(1-methyl-

1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (0.26 g) obtained in Working example 33, and the system was agitated for 1 hour 30 minutes at 100°C. The reaction solution was concentrated, ethanol was added to the residue and the resulting system was concentrated to achieve crystallisation. The crude crystals were recrystallised from methanol, isopropyl alcohol and ether to obtain 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline 2-hydrochloride (0.193 g). M.p. 168-178°C

IR (Nujol): 2900, 1695, 1585, 1035 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 3.16 (2H, m), 3.40 (2H, m), 3.83 (3H, s), 3.80 (2H, m) 4.76 (1H, m), 7.03 (2H, broad s), 7.30 (4H, m), 9.3-10.3 (2H, m)

Elementary analysis: $C_{12}H_{16}N_6 \cdot 2HCl \cdot 0.25$isopropyl alcohol

Calculated values: C 46.09; H 6.06; N 25.29; Cl 21.34 (%)

Experimental values: C 46.29; H 6.16; N 25.45; Cl 21.26 (%)

Working example 35

N,N-dimethylformamide (17 ml) was added to the 2-benzyloxycarbonyl-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (1.75 g) obtained in Working example 33, then the system was cooled at 5°C and methyl iodide (1 ml) was added. Sodium hydride (65%) (0.22 g) was added and the system was agitated for 3 hours at 5°C. Iced water was added to the reaction solution, and extraction was performed 3 times using methylene chloride. The methylene chloride layers were washed twice using water, washed once using saturated salt solution, dried using anhydrous magnesium sulfate then concentrated under reduced pressure. The resulting oil was purified by silica gel column chromatography (30 g of silica gel), with ethyl acetate:methylene chloride (15:85) as the elution solvent), to obtain 2-benzyl-

oxycarbonyl-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)-aminomethyl]-1,2,3,4-tetrahydroisoquinoline (1.73 g) as an oil.

IR ($CHCl_3$): 1680, 1580 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.86 (2H, m), 3.16 (3H, broad s), 3.0-4.3 (4H, m), 3.80 (3H, s), 5.07 (2H, s), 5.46 (1H, dd, J = 5.0 Hz, J = 7.0 Hz), 7.3 (9H, m)

Working example 36

2-Benzyloxycarbonyl-1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline (1.6 g) was agitated in acetic acid (12 ml) and concentrated hydrochloric acid (10 ml) for 1 hour 30 minutes at 100°C. The reaction solution was concentrated, and the resulting oil was dissolved in water, neutralised using solid sodium hydrogen carbonate, then extracted 3 times using methylene chloride. The methylene chloride layers were washed once using water and once using saturated salt solution, dried using anhydrous sodium sulfate, then concentrated under reduced pressure to obtain a crystalline residue (1.06 g). The crude crystals were dissolved in methanol (30 ml) with heating, then fumaric acid (0.45 g) was added and the system was agitated. The solution was concentrated to 10 ml, then left to stand. The precipitated crystals were filtered, and washed using methanol to obtain 1.2 g of crystals. These crystals were recrystallised from water and isopropyl alcohol to obtain 1-[N-methyl-N-(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline fumarate (0.9 g).

M.p. 196-197°C

IR (Nujol): 1700, 1585 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.9-3.6 (4H, m), 3.16 (3H, s), 3.6-4.2 (2H, m), 3.96 (3H, s), 4.63 (1H, m), 6.50 (2H, s), 7.26 (4H, broad s), 8.10 (3H, broad s)

Elementary analysis: $C_{17}H_{22}N_6O_4$

Calculated values: C 54.53; H 5.92; N 22.45 (%)

Experimental values: C 54.46; H 5.82; N 22.23 (%)

Working example 37

(a) Production of the starting material compound (1)

An aqueous (200 ml) solution of potassium cyanide (39.6 g) was added to a methylene chloride (340 ml) solution of 5,7-dimethoxyisoquinoline (23 g), then benzoyl chloride (85.4 g) was added at 0°C over a period of 2 hours with agitation, after which the reaction mixture was gradually returned to room temperature. It was agitated for a further 3 hours at room temperature, then the methylene chloride layer was separated, washed 3 times using aqueous 1% sodium hydroxide solution (300 ml), washed using water, then dried using magnesium sulfate. The solvent was distilled off, and the resulting residue was crystallised using ethanol and ether, then obtained by filtration. The crude crystals were recrystallised from a mixture of ethanol and chloroform to obtain 2-benzoyl-1-cyano-5,7-dimethoxy-1,2-dihydroisoquinoline (23 g).

M.p. 163-165°C

IR (Nujol): 1660, 1600, 1575 cm^{-1}

NMR δ (ppm) ($CDCl_3$): 3.87 (6H, s), 6.35 (1H, d, J = 8 Hz), 6.50 (1H, s), 6.53 (2H, s), 6.55 (1H, d, J = 8 Hz), 7.57 (5H, m)

(b) Production of the starting material compound (2)

An N,N-dimethylformamide (150 ml) solution of the 2-benzoyl-1-cyano-5,7-dimethoxy-1,2-dihydroisoquinoline (23 g) obtained above was added dropwise over a period of 25 minutes at from -10°C to -8°C to a dimethylformamide (172 ml) suspension of (50%) sodium hydride (8.3 g), in a current of nitrogen. A dimethylformamide (50 ml) solution of methyl iodide (51 g) was added dropwise to this over a period of 30 minutes, and the resulting system was agitated for 2 hours. The reaction mixture was poured

into iced water, extracted using ethyl acetate, washed using water and dried using magnesium sulfate. The solvent was distilled off to obtain a residue, which was dissolved in dioxane (600 ml), then 5% aqueous sodium hydroxide solution (270 ml) was added and the system was agitated for 30 minutes at 50°C. The solvent was distilled off under reduced pressure, the residue was extracted using methylene chloride, and the extract solution was washed using water then dried using magnesium sulfate. The solvent was distilled off to obtain crude 5,7-dimethoxy-1-methylisoquinoline. This was subjected to silica gel chromatography, and the crystals obtained from the chloroform-ethyl acetate runoff were recrystallised from ethanol to obtain 5,7-dimethoxy-1-methylisoquinoline (9.75 g).

M.p. 88-91°C

IR (Nujol): 1675, 1620 cm^{-1}

NMR δ (ppm) ($CDCl_3$): 2.87 (3H, s), 3.93 (6H, s), 6.48 (1H, d, J = 2 Hz), 7.18 (1H, d, J = 2 Hz), 7.80 (1H, d, J = 6 Hz), 8.32 (1H, d, J = 6Hz)

(c) Production of the starting material compound (3)

The 5,7-dimethoxy-1-methylisoquinoline (9.7 g) obtained above and selenium dioxide (7.92 g) were added to dioxane (80 ml), and the system was refluxed with agitation for 2 hours. After cooling, the solvent was distilled off under reduced pressure and the residue was extracted using methylene chloride. The solvent was distilled off and ethanol (200 ml) was added to the residue, and the insolubles were separated by filtration. The solvent was distilled off from the filtrate and the residue was dissolved in a small amount of chloroform, then subjected to silica gel column chromatography; the crystals obtained from the ethyl acetate-chloroform runoff were

recrystallised from ethanol-chloroform to obtain 5,7-dimethoxyisoquinoline-1-carbaldehyde (4.6 g).

M.p. 132-133°C

IR (Nujol): 1690, 1620 cm^{-1}

NMR δ (ppm) ($CDCl_3$): 3.92 (6H, s), 6.55 (1H, d, J = 2 Hz), 8.05 (1H, d, J = 6 Hz), 8.13 (1H, d, J = 2 Hz), 8.53 (1H, d, J = 6 Hz), 10.30 (1H, s)

(d) Production of the target compound

5,7-dimethoxyisoquinoline-1-carbaldehyde (4.5 g), 1-methyl-1H-tetrazol-5-amine (2.05 g) and a small amount of piperazine catalyst were added to toluene (110 ml), and the resulting system was refluxed for 14 hours. After cooling, crystals were obtained by filtration, then dissolved in hot chloroform, the insolubles were obtained by filtration, and the filtrate was dried to solid to obtain 5,7-dimethoxy-1-[(1-methyl-1H-tetrazol-5-yl)amino-methyl]isoquinoline (4.6 g). This was suspended in dioxane (200 ml), platinum oxide (2 g) was added, catalytic reduction was allowed to proceed under atmospheric pressure, the catalyst was removed by filtration, and the filtrate was dried to solid and converted to a powder using ethanol-ether. The powder was suspended in chloroform, agitated for 30 minutes, then obtained by filtration to obtain 5,7-dimethoxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]isoquinoline (1.05 g).

M.p. 217-220°C (degradation)

IR (Nujol): 3250, 1625 cm^{-1}

NMR δ (ppm) ($CDCl_3$): 3.80 (3H, s), 3.87 (3H, s), 3.97 (3H, s), 5.08 (2H, d, J = 6 Hz), 6.87 (1H, d, 2 Hz), 7.13 (1H, d, J = 2Hz), 7.40 (1H, t, J = 6 Hz), 7.80 (1H, d, J = 6 Hz), 8.28 (1H, d, J = 6 Hz)

The filtrate obtained with the above-mentioned compound was evaporated to dryness, suspended in ethyl acetate and

agitated for 30 minutes to obtain 5,7-dimethoxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethylene]-1,2-dihydroisoquinoline (2.15 g).

M.p. 225-230°C (degradation)

IR (Nujol): 1620, 1580 cm^{-1}

Mass spectrum: M^+ 300

NMR δ (ppm) ($CDCl_3$): 3.63 (3H, s), 3.80 (3H, s), 3.93 (3H, s), 6.17 (1H, d, J = 8 Hz), 6.55 (1H, d, J = 2 Hz), 6.60 (1H, d, J = 8 Hz), 6.93 (1H, d, J = 2 Hz), 7.77 (1H, d, J = 6 Hz), 7.97 (1H, d, J = 6 Hz)

Working example 38

The 5,7-dimethoxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethylene]-1,2-dihydroisoquinoline (1.55 g) obtained in Working example 37 was added to hydroiodic acid (62 ml) and the resulting system was refluxed for 8 hours. The solvent was distilled off under reduced pressure, sodium hydrogen carbonate was added to neutralise the system, which was then filtered and dried to obtain 1-(1-methyl-1H-tetrazol-5-yl)aminomethyl-5,7-dihydroxyisoquinoline (550 mg).

M.p. 225-257°C (degradation) (hydrochloride)

IR (Nujol): 3300, 1685, 1620 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 3.82 (3H, s), 4.95 (2H, d, J = 6 Hz), 6.77 (1H, d, J = 2 Hz), 6.90 (2H, d, J = 2 Hz), 7.33 (1H, t, J = 6 Hz), 7.77 (1H, d, J = 6 Hz), 8.17 (1H, d, J = 6 Hz), 9.33 (1H, s), 10.50 (1H, s)

Working example 39

The 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-5,7-dihydroxyisoquinoline (520 mg) obtained in Working example 38 and platinum oxide (500 mg) were added to a mixture of dimethylformamide (125 mg) and acetic acid (30 ml), and moderate pressure catalytic reduction was allowed to proceed for 10 hours under 3 atmospheres pressure. The catalyst was removed by filtration, the solvent was

distilled off under reduced pressure, and hydrochloric acid ethanol was added to the residue, then the precipitated crystals were obtained by filtration, water was added and the insolubles were removed by filtration, and the filtrate was concentrated then passed through a column packed with HP-20 (adsorbent resin, Mitsubishi Kasei) (75 ml). The substance obtained from the cold water runoff was crystallised from ethanol and obtained by filtration, to obtain 1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (240 mg).

M.p. 257°C (degradation)

IR (Nujol): 3250, 1610, 1600 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.60-3.00 (2H, m), 3.0-3.90 (4H, m), 3.83 (3H, s), 4.60 (H1, m), 6.27 (H1, d, J = 2 Hz), 6.40 (1H, d, J = 2 Hz), 7.67-(1H, t, J = 6 Hz), 9.00-10.0 (4H, broad)

Elemental analysis: $C_{12}H_{16}O_2N_6 \cdot HCl$

Calculated values: C 46.08; H 5.48; N 26.87

Experimental values: C 45.68; H 5.46; N 27.10

Working example 40

The 5,7-dimethoxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]isoquinoline (540 mg) obtained in Working example 37(d) and platinum oxide (500 mg) were added to a mixture of N,N-dimethylformamide (100 ml) and acetic acid (50 ml), and moderate pressure catalytic reduction was allowed to proceed for 7 hours under 3 atmospheres pressure. The catalyst was removed by filtration, the solvent was distilled off under reduced pressure and the residue was washed using ether, then obtained by filtration, to obtain 5,7-dimethoxy-1-[(1-methyl-1H-tetrazol-5-yl)aminomethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (55 mg).

M.p. 188-190°C (degradation)

IR (Nujol): 1625, 1585 cm^{-1}

NMR δ (ppm) (DMSO-d_6): 2.86 (3H, s), 2.30-2.60 (2H, m), 2.60-3.30 (2H, m), 3.30-4.30 (3H, m), 3.80 (3H, s), 3.85 (6H, s), 6.10 (2H, s), 6.40 (2H, s), 7.10 (1H broad)

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Translator's note

Japanese proper nouns can have several possible readings; common readings have been chosen throughout.